Inflammatory eruptions associated with immune checkpoint inhibitor therapy: A single-institution retrospective analysis with stratification of reactions by toxicity and implications for management

Emily Coleman, BA,[a] Christine Ko, MD,[a,b] Feng Dai, PhD, MS,[c] Mary M. Tomayko, MD, PhD,[a] Harriet Kluger, MD,[d] and Jonathan S. Leventhal, MD[a]
New Haven, Connecticut

Background: There is increasing recognition of distinct inflammatory eruptions associated with checkpoint inhibitors. A better understanding of their severity, therapeutic response, and impact on cancer treatment is needed.

Objective: To analyze the different rashes associated with immunotherapy referred to our institution's oncodermatology clinic and inpatient consultative service and to evaluate their therapeutic response and impact on immunotherapy.

Methods: We retrospectively reviewed the medical records of patients referred to the oncodermatology clinic or inpatient dermatology service during 2016-2018 at Yale-New Haven Hospital for eruptions that developed during immunotherapy.

Results: In total, 98 patients (51 men, 47 women) treated with checkpoint inhibitors developed 103 inflammatory eruptions, with a range of mean latency of 0.2-17.7 months. A minority of patients (25/103; 24.3%) required immunotherapy interruption; most of these cases involved immunobullous (7/8; 87.5%), lichenoid (8/26; 30.8%), maculopapular (6/18; 33.3%), and Stevens-Johnson syndrome–like (2/2, 100%) reactions. Only 3 of 16 (18.8%) patients who had their immunotherapy interrupted had a grade 2 or 3 flare on rechallenge. Most reactions (93/103; 90.3%) responded to dermatologic therapy or immunotherapy interruption.

Limitations: This was a retrospective study from a single tertiary care center.

Conclusion: A variety of inflammatory reactions might occur from immunotherapy with differing degrees of severity. While most rashes responded to topical treatment, immunobullous and exfoliative presentations frequently interrupted immunotherapy. Increased awareness and early recognition could reduce the need for unnecessary immunotherapy interruption. (J Am Acad Dermatol 2019;80:990-7.)

From the Departments of Dermatology,[a] Pathology,[b] Yale Center for Analytical Sciences,[c] and Internal Medicine (Medical Oncology),[d] Yale University School of Medicine, New Haven.

Funding sources: Supported in part by a National Institutes of Health medical student research fellowship (to Ms Coleman) and immune checkpoint inhibitor toxicity grant (R01 CA227473, to Dr Kluger).

Conflicts of interest: Dr Kluger served on an advisory board or received consultant fees from Roche-Genentech, Corvus, Nektar, Biodesix, Iovance, Pfizer, and Celldex and received research support from Bristol Meyers Squibb, Merck, Apexigen, and the NIH for immunotherapy toxicities. Dr Leventhal served on an advisory board for Amgen. All other authors have no conflicts of interest to disclose.

Accepted for publication October 28, 2018.

Reprint requests: Jonathan S. Leventhal, MD, 15 York St, LMP 5040, New Haven, CT 06510. E-mail: jonathan.leventhal@yale.edu.

Published online November 3, 2018.
0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2018.10.062

Key words: cutaneous adverse events; cytotoxic T-lymphocyte associated protein 4; dermatologic toxicities; immune checkpoint inhibitor; immune-related adverse events; immunotherapy; programmed cell death 1; programmed cell death ligand 1.

CAPSULE SUMMARY

- Cutaneous reactions commonly develop during immunotherapy, and a variety of inflammatory patterns have been observed.
- In this cohort, 25 of 103 (24.3%) rashes, most commonly those of immunobullous and exfoliative presentations, required interruption of immunotherapy.
- There are key distinctions among the rashes that develop from checkpoint inhibitors with regards to severity and impact on cancer treatment.

Immune checkpoint inhibitors are a powerful new class of anticancer drugs that leverage the immune system to promote antitumoral activity. Monoclonal antibodies directed against programmed cell death 1 (PD-1; eg, nivolumab, pembrolizumab), programmed cell death ligand 1 (PD-L1; eg, atezolizumab, durvalumab, avelumab), and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4; eg, ipilimumab) have been approved for use in multiple cancer types.[1-3] Sustained antitumoral responses can be elicited but immune-related adverse events (irAE) affecting multiple organs might be triggered as well.[4-6] As dermatologic irAE are among the most frequently reported,[4,7-9] dermatologists have an important role in evaluating and managing these toxicities.

Over the past several years, specific inflammatory eruptions have emerged among the cutaneous irAE, including lichenoid reactions, maculopapular eruptions, immunobullous eruptions, and Stevens-Johnson syndrome (SJS).[7-13] Clinical trials have demonstrated that cutaneous irAE of any grade are more likely to develop during combination anti–CTLA-4 anti–PD-1 therapy (ie, 40.3% of melanoma patients on nivolumab and ipilimumab) than during monotherapy with anti–PD-1 (25.9% of melanoma patients on nivolumab) or anti–CTLA-4 (32.8% of melanoma patients on ipilimumab) alone.[14] Most studies have not differentiated between the types of rashes observed.[14] Detailed information about their therapeutic impact, response to treatment, and prognostic implications is profoundly lacking. This study aims to analyze the rashes associated with immunotherapy referred to the oncodermatology clinic and inpatient consultative service at our institution and evaluate their therapeutic response and impact on immunotherapy.

METHODS

After approval from the institutional review board, medical records of patients treated by the oncodermatology clinic and inpatient consultative service at Yale New Haven Hospital during January 2016-January 2018 were obtained from the electronic health record data system. Patients referred to dermatology for eruptions that developed during treatment with the Food and Drug Administration–approved checkpoint inhibitors (nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, and ipilimumab) were identified. The medical records were reviewed and analyzed for patient demographics, medical history, medications, clinical morphology of skin lesions, presence or absence of pruritus, grade of rash, latency, skin biopsy, direct immunofluorescence and indirect immunofluorescence studies (if performed), clinical diagnosis as documented in the dermatology note, treatment of rash, response of rash, date of cycle 1, impact of rash on immunotherapy (none, temporarily interrupted, discontinued), evolution of rash on retreatment with immunotherapy (if applicable), and other irAE.

Grade of rash was determined by Common Terminology Criteria for Adverse Events, version 4: a grade 1 rash covered <10% of the body surface area (BSA), a grade 2 rash covered 10%-30% of the BSA with or without symptoms affecting functional activities of daily living; a grade 3 rash covered >30% of the BSA with or without symptoms affecting self-care activities of daily living; and a grade 4 rash represented life-threatening rash (eg, exfoliative dermatitis) requiring hospitalization or intensive care.[4]

RESULTS

Demographics and setting

In this cohort, 98 patients (51 males, 47 females) with 103 inflammatory eruptions occurring during treatment with immunotherapy during 2016-2018 were referred to dermatology at our tertiary care center. Of 103 rashes, 88 (85%) were evaluated in the outpatient oncodermatology clinic and 15 (15%) by the inpatient consultative service. The most

Abbreviations used:

AGEP:	acute generalized exanthematous pustulosis
BSA:	body surface area
CTLA-4:	cytotoxic T-lymphocyte–associated protein 4
irAE:	immune-related adverse events
PD-1:	programmed cell death 1
PD-L1:	programmed cell death ligand 1
PRP:	pityriasis rubra pilaris
SJS:	Stevens-Johnson syndrome
UVB:	ultraviolet B

frequently associated cancer types were lung cancer (n = 44), melanoma (n = 33), and renal cell carcinoma (n = 7). Other malignancies (n = 19) included acute myelogenous leukemia, gastrointestinal, gynecological, head and neck, glioblastoma, genitourinary, Hodgkin lymphoma, and Merkel cell carcinoma.

Rashes were most commonly associated with the anti–PD-1 agents pembrolizumab (35/103 rashes) and nivolumab (33/103), followed by combination anti–CTLA-4 anti–PD-1 therapy with ipilimumab and nivolumab (17/103). The anti–PD-L1 agents atezolizumab (8/103) and durvalumab (5/103) and anti–CTLA-4 drug ipilimumab (5/103) were associated with fewer inflammatory eruptions referred to dermatology.

In total, 9 of 98 (9%) patients had a pre-existing dermatosis that was quiescent before immunotherapy but that subsequently flared during treatment; psoriasis was the most common (7/9). Table I summarizes the demographics, rash characteristics, associated immunotherapy class, and other irAEs.

Rash diagnosis, latency, and grade

Diagnoses were rendered clinically (50/103) or by clinicopathologic correlation (53/103). Inflammatory reactions were categorized as lichenoid (26/103, 25%), maculopapular or exanthematous (18/103, 18%), psoriasiform (17/103, 17%), eczematous (12/103, 12%), immunobullous (8/103, 8%),[15,16] prurigo simplex and nodularis (7/103, 7%), Grover-like (4/103, 4%), acneiform (4/103, 4%), granulomatous (3/103, 3%),[17] SJS-like (2/103, 2%), pityriasis rosea–like (1/103, 1%), or pityriasis rubra pilaris (PRP)–like (1/103, 1%).[18]

In patients with lung cancer, the most common reactions were lichenoid (n = 10), maculopapular (n = 9), and psoriasiform (n = 7), and in patients with melanoma, the most common reactions were lichenoid (n = 8), eczematous (n = 7), and psoriasiform (n = 6). Overall no trends were observed between tumor and rash type.

Mean latency to onset varied according to rash type. Maculopapular, pityriasis rosea–like, PRP-like, and SJS-like eruptions had the shortest mean latency, ranging 0.2-1.4 months. Conversely, lichenoid, eczematous, psoriasiform, immunobullous, acneiform, prurigo simplex and nodularis, and granulomatous reactions had a longer mean latency, ranging 4-18 months. One case of SJS-like reaction initially manifested with clinical and histopathologic features of acute generalized exanthematous pustulosis (AGEP); then 2 weeks later, Nikolsky sign and sloughing of mucosal and cutaneous surfaces developed consistent with AGEP/SJS-like phenotype.

Of 103 rashes, 53 (51%) were grade 1, 30 (29%) grade 2, 18 (17%) grade 3, and only 2 grade 4. Immunobullous (median grade 3), SJS-like (median grade 4), and PRP-like (grade 3) erythrodermic eruptions had the highest-grade presentations, followed by maculopapular eruptions (median grade 2). Low-grade eruptions rarely progressed to grade 3 or 4 rashes; however, a few cases of lichenoid, maculopapular, bullous pemphigoid, and AGEP/SJS-like reactions progressed from a grade 1 or 2 presentation to a grade 3 or 4. No patients died due to dermatologic toxicity.

Morphology of rash

The predominant morphology of the 5 most common rash types (lichenoid, maculopapular, psoriasiform, eczematous, and immunobullous) are described. Three fourths of eruptions had associated pruritus, regardless of grade. Table II summarizes the morphologic descriptions and severity of the different rash types.[16-18]

Overall, checkpoint inhibitor–associated rashes shared clinical features with classic dermatologic eruptions. Lichenoid reactions had lichen planus–like characteristics, including violaceous scaly papules, oral or genital ulcers, leukoplakia, hypertrophic plaques, and nail dystrophy. Maculopapular eruptions were similar to typical exanthematous drug eruptions secondary to antibiotics. Psoriasiform eruptions were similar to multiple subtypes of psoriasis, including plaque psoriasis with well-defined red-pink papules and plaques with silvery scales over extensor extremities, seborrheic plaques on the face and scalp, pustules, inverse plaques, palmoplantar involvement, and widespread guttate papules. Eczematous reactions presented with erythematous scaly macules and papules and involved localized patches and plaques, nummular plaques, dyshidrotic vesicles, or asteatotic eczema. Immunobullous disorders similarly mimicked the diversity of presentations that can be observed with autoimmune blistering disorders,

Table I. Summary of patient demographics, associated immunotherapy class, rash characteristics, and other irAE

	Demographics		Immunotherapy class, n			Rash characteristics			
Rash type	No. patients, (M, F)	Age, y, mean	Anti–CTLA-4	Anti–PD-1 or PD-L1	Both	Latency, mon, mean (range)	Pruritus, n	Grade, median (range)	Other irAE,* n
Lichenoid	26 (17, 9)	64	2	23	1	6.2 (0.5-20)	25	1 (1-3)	9
Maculopapular	18 (5, 13)	61	2	11	5	1.0 (0.2-5.7)	16	2 (1-3)	7
Psoriasiform	17 (8, 9)	67	1	12	4	5.7 (0.2-28.8)	10	1 (1-3)	8
Eczematous	12 (6, 6)	66	0	9	3	5.8 (0.6-25)	12	1 (1-3)	5
Immunobullous	8 (4, 4)	68	0	8	0	4.5 (0.5-10)	8	3 (2-3)	2
Prurigo	7 (3, 4)	71	0	6	1	10.1 (1.8-16)	7	1 (1-3)	3
Grover-like	4 (4, 0)	71	0	4	0	4.2 (0.2-14.4)	4	1 (1-2)	1
Acneiform	4 (3, 1)	47	0	4	0	4.3 (0.2-11)	1	1 (1-2)	1
Granulomatous	3 (0, 3)	65	0	2	1	17.7 (7-36)	0	1	0
SJS-like	2 (1, 1)	62	0	0	2	1.4	2	4	2
PR-like	1 (1, 0)	75	0	1	0	0.2	1	2	0
PRP-like	1 (1, 0)	63	0	1	0	0.46	1	3	0
Total	103 (54, 49)	65	5	81	17	5.13 (0.1-36)	77	1 (1-4)	36†

AGEP, Acute generalized exanthematous pustulosis; *CTLA-4*, cytotoxic T-lymphocyte–associated protein 4; *irAEs*, immune-related adverse events; *PD-1*, programmed cell death 1; *PD-L1*, programmed cell death ligand 1; *PR*, pityriasis rosea; *PRP*, pityriasis rubra pilaris; *SJS*, Stevens-Johnson syndrome.

*Other irAE included adrenalitis, acute interstitial nephritis, colitis, hepatitis, hypophysitis, pneumonitis, thyroiditis, vitiligo, autoimmune hemolytic anemia, arthritis, aseptic meningitis, encephalitis, fatigue, pancreatitis, and uveitis.

†A total of 36 patients (2 patients had multiple rash types).

including tense vesicles and bullae but also urticarial lesions, oral erosions, dyshidrosiform vesicles, and annular configurations.[16]

Histopathologic analysis

Biopsies were obtained in 53 of 103 (51%) rashes and evaluated by Yale dermatopathologists. Additional direct and indirect immunofluorescence studies were performed if vesicles or bullae were present or if patients had refractory pruritus. The most commonly biopsied rashes were lichenoid, immunobullous, psoriasiform, maculopapular, and eczematous reactions. Lichenoid interface dermatitis was the most frequent histopathologic diagnosis (16/53 biopsies, 30%). Histopathologic features of the different rash types are summarized in Table III.[16-18]

Treatment of rash

Treatment of eruptions varied according to severity. In our study, 93 of 103 (90%) rashes were treated with topical corticosteroids; 21 of 103 (20%) required systemic corticosteroids. Immunobullous (8/8), SJS-like (2/2), PRP-like erythroderma (1/1), maculopapular (4/18), and lichenoid reactions (3/26) had the highest associated use of systemic corticosteroids. Other treatments included acitretin, phototherapy with narrowband ultraviolet B (UVB), and intralesional kenalog for lichenoid reactions; phototherapy with narrowband UVB, acitretin, and methotrexate for psoriasiform eruptions; doxycycline with or without niacinamide, omalizumab, methotrexate, and dapsone for immunobullous eruptions[15,16]; and infliximab for the 2 SJS-like eruptions, both of which had associated colitis. Management of pruritus, the most frequently associated symptom, was an integral component of dermatologic care and included topical corticosteroids, topical camphor-menthol, antihistamines, gabapentin, pregabalin, and aprepitant.

In total, 93 of 103 (90%) rashes (including those that flared on subsequent immunotherapy infusions) improved with dermatologic therapy, interruption of immunotherapy, or both. Only 10 of 103 (10%) rashes did not respond to dermatologic treatment and interruption of immunotherapy. Further, 2 cases of lichenoid reactions and 1 case of prurigo nodularis persisted at least 6 months after cessation of immunotherapy (through the most recent follow-up). Table IV summarizes the dermatologic treatments, response of rash to therapy, and associated impact on cancer therapy.[16-18]

Impact on immunotherapy

Interruption of checkpoint inhibitor therapy occurred in multiple rash types because of the eruption severity. In total, 16 of 103 cases (15.5%) resulted in temporary interruption and 9 of 103 (8.7%) resulted in permanent discontinuation. There was a statistically significant association between high-grade rash (grade 3 or 4) and

Table II. Summary of clinical presentations of inflammatory eruptions to checkpoint inhibitor therapy

Rash type	Predominant morphology (n)	Other presentations (n)	Pruritus, n	Grade, n			
				1	2	3	4
Lichenoid	Pink-to-violaceous papules with scale (18)	Oral or genital ulcers (6), leukoplakia (2), hypertrophic plaques (4), vesicles (3), koebnerization (2), inflamed seborrheic keratoses (1), dystrophic nails (1), papulopustules (1), palmoplantar (3), inverse (2), generalized papular (1)	25	17	7	2	0
Maculopapular	Erythematous macules and papules (18)	Erythroderma (1), photoaccentuated (1), urticarial (1)	16	3	11	4	0
Psoriasiform	Pink-red papules with silvery scale (17)	Localized extensor (7), scalp and facial (4), palmoplantar pustulosis (2), inverse (2), widespread guttate and plaques (2), psoriatic arthritis (1)	10	12	4	1	0
Eczematous	Erythematous scaly macules and papules (11)	Nummular plaques (4), asteatotic eczema (1), dyshidrotic (1)	12	7	3	1	0
Immunobullous[16]	tense vesicles and bullae (7)	Pruritic papules with erosions (2), oral ulceration (1), urticarial-predominant (1), dyshidrosiform (1), annular plaques with peripheral vesicles (LABD, 1)	8	0	1	7	0
Prurigo	Linear erosions with crust (5)	Prurigo nodules (1), lichen simplex chronicus (1)	7	4	1	2	0
Grover-like	Erythematous papules with scale (4)	Papulovesicles (1)	4	3	1	0	0
Acneiform	Inflammatory papules and pustules (3)	Rosacea (2), flare of papulopustular eruption that previously developed during cetuximab (1)	1	3	1	0	0
Granulomatous[17]	Erythematous firm dermal papules (2)	Annular plaques with papular edge (granuloma annulare, 1)	0	3	0	0	0
SJS-like	Dusky erythematous macules, moist desquamation, mucosal ulcerations, Nikolsky sign (2)	Preceding erythematous plaques with pustules (culture negative) (1)	2	0	0	0	2
PR-like	Pink oval macules and papules with trailing scale (1)		1	0	1	0	0
PRP-like[18]	Erythroderma with orange waxy keratoderma (1)		1	0	0	1	0

LABD, Linear IgA bullous dermatosis; *PR*, pityriasis rosea; *PRP*, pityriasis rubra pilaris; *SJS*, Stevens-Johnson syndrome.

interruption or discontinuation of immunotherapy ($P < .05$), as expected.

Immunotherapy was immediately discontinued in 2 patients with grade 4 SJS-like reactions and in the 1 patient with intolerable grade 3 toxicity from PRP-like erythroderma.[18] As a group, immunobullous eruptions most commonly required either temporary interruption (3/8 patients) or permanent discontinuation (4/8 patients) of checkpoint inhibitor therapy due to either grade 3 toxicity, mucosal involvement, or intolerable symptoms of pruritus.[16] Less commonly, lichenoid (8/26 patients) and maculopapular (6/18 patients) eruptions resulted in interruption of treatment. Only 1 of 17 psoriasiform

Table III. Summary of histopathologic diagnoses associated with inflammatory eruptions to checkpoint inhibitor therapy

Clinical diagnosis	Patients, n	Corresponding histologic diagnoses (n)
Lichenoid	16	Lichenoid interface dermatitis (15), scattered foci of histiocytes and lymphocytes with epidermal collarettes (lichen nitidus-like) (1)
Eczematous	5	Eosinophilic spongiosis (5)
Maculopapular	7	Dermal hypersensitivity reaction (5), acute vacuolar dermatitis (1), lichenoid interface dermatitis with eosinophils (1)
Psoriasiform	4	Psoriasiform (4)
Immunobullous[16]	8	Subepidermal bulla with eosinophils (4), subepidermal bulla with focal interface changes (1), eosinophilic spongiosis (1), erosion of epidermis with eosinophils (1), subepidermal bulla with neutrophils (LABD, 1) DIF: linear IgG and C3 at the DEJ (5), linear IgG and C3 and IgA at the DEJ (LABD, 1) IIF: serum linear deposition of IgG at DEJ of monkey esophagus (2), serum intercellular staining of IgG and IgA on monkey esophagus with 1:10 (IgA) and 1:80 (IgG) dilutions (LABD, 1)
Prurigo nodularis	1	Epidermal acanthosis and parakeratosis (1)
Grover-like	2	Epidermal acantholysis and dyskeratosis (2)
Acneiform	1	Suppurative and granulomatous folliculitis (1)
Granulomatous[17]	3	Naked granulomas within the dermis with multinucleated cells (sarcoidosis-like, 2), superficial and deep perivascular and interstitial infiltrate of histiocytes and lymphocytes with focal palisading (granuloma annulare-like, 1)
SJS-like	2	Epidermal necrosis with numerous apoptotic keratinocytes and lymphoplasmacytic inflammation (SJS-like, 1), subcorneal pustules and mixed infiltrate with eosinophils and necrotic keratinocytes, and lichenoid interface dermatitis with necrotic keratinocytes (AGEP and SJS-like, 1).
PR-like	1	Patchy papillary dermal mixed infiltrate with plasma cells and eosinophils with red cell extravasation (1)
PRP-like[18]	1	Epidermal acanthosis with orthokeratosis and parakeratosis, intact granular layer and mild spongiosis, perivascular inflammatory infiltrate within the superficial dermis (1)

AGEP, Acute generalized exanthematous pustulosis; *C3*, complement 3; *DEJ*, dermal-epidermal junction; *DIF*, direct immunofluorescence; *IIF*, indirect immunofluorescence; *LABD*, linear IgA bullous dermatosis; *PR*, pityriasis rosea; *PRP*, pityriasis rubra pilaris; *SJS*, Stevens-Johnson syndrome.

rashes resulted in interruption of treatment, but this patient had both grade 3 rash and colitis. Presentation of prurigo simplex or nodularis, Grover-like, acneiform, granulomatous, and pityriasis rosea–like eruptions had no effect on immunotherapy in this cohort.

Of the 16 eruptions that resulted in temporary interruption of immunotherapy because of rash severity, only 3 cases (lichenoid, maculopapular, and bullous pemphigoid) had a grade 2 or 3 flare on rechallenge with checkpoint inhibitor therapy. The others resolved or remained well controlled (grade 1) on dermatologic therapy and continued checkpoint inhibitor therapy.

DISCUSSION

This study summarizes data on 103 inflammatory eruptions that developed during checkpoint inhibitor therapy at a tertiary care center. This relatively large cohort supports previous literature on the diversity of associated dermatologic toxicities[7-13,16,17,19-21]; the top 5 diagnoses were lichenoid, maculopapular, psoriasiform, eczematous, and immunobullous reactions. Our series adds several important findings related to severity, therapeutic response, and effect on cancer treatment.

Of the distinct rash types, immunobullous reactions most frequently required treatment interruption, followed by lichenoid, maculopapular, and SJS-like reactions. Overall, ~25% of rashes required interruption of immunotherapy, underscoring the substantial impact of cutaneous toxicity on oncologic care. This rate is similar to previously reported smaller series.[9,13] Importantly, it was safe to restart immunotherapy in patients whose treatment was temporarily interrupted because of a grade 2 or 3 rash; most eruptions resolved on their own or remained low grade and controlled on dermatologic therapy when checkpoint inhibitor therapy was resumed.

Table IV. Summary of rash treatment, therapeutic response, and impact on cancer therapy

Rash type (n)	Rash treatment (n)	Rash improved, n, yes/no	Impact on immunotherapy, n		
			None	Temporarily interrupted	Permanently discontinued
Lichenoid (26)	Topical steroids (25), systemic steroids (3), camphor-menthol (5), antihistamines (4), gabapentin (3), topical tacrolimus (3), narrowband UVB phototherapy (2), acitretin (1), doxycycline (1), intralesional kenalog (1)	23/3	18	6	2
Maculopapular (18)	Topical steroids (18), systemic steroids (4), antihistamines (1), camphor-menthol (1), gabapentin (1)	17/1	12	6	0
Psoriasiform (17)	Topical steroids (16), systemic steroids (1), ketoconazole shampoo (4), narrowband UVB phototherapy (2), acitretin (2), antihistamines (2), topical tacrolimus (2), camphor-menthol (1), gabapentin (1), intralesional kenalog (1), methotrexate 15 mg/wk (1)	16/1	16	1	0
Eczematous (12)	Topical steroids (12), systemic steroids (1), camphor-menthol (5), antihistamines (4), gabapentin (3), topical tacrolimus (3), narrowband UVB phototherapy (2)	11/1	12	0	0
Immunobullous (8)[16]	Topical steroids (8), systemic steroids (8), doxycycline (2), doxycycline and niacinamide (2), omalizumab (2), dapsone (1), methotrexate (1)	8/0	1	3	4
Prurigo (7)	Topical steroids (5), systemic steroids (1), antihistamines (4), camphor-menthol (3), gabapentin (3), aprepitant (1)	6/1	7	0	0
Grover-like (4)	Topical steroids (4), antihistamines (2), camphor-menthol (2)	3/1	4	0	0
Acneiform (4)	Topical steroids (1), doxycycline (1), clindamycin lotion (1), metronidazole cream (1)	4/0	4	0	0
Granulomatous (3)[17]	Topical steroids (2)	1/2	3	0	0
SJS-like (2)	Topical steroids (2), systemic steroids (2), infliximab (2)	2/0	0	0	2
PR-like (1)	Topical steroids (1)	1/0	1	0	0
PRP-like (1)[18]	Topical steroids (1), systemic steroids (1), acitretin (1)	1/0	0	0	1

PR, Pityriasis rosea; *PRP*, pityriasis rubra pilaris; *SJS*, Stevens-Johnson syndrome; *UVB*, ultraviolet B.

Interestingly, we found that 9% (9/98) of patients had a pre-existing dermatosis (most commonly psoriasis) that flared on immunotherapy. In addition, there was a wide range in mean latency (0.2-17.7 months) among the inflammatory eruptions; in general, granulomatous, lichenoid, psoriasiform, eczematous, and immunobullous rashes had a longer latency than maculopapular and SJS-like eruptions. Importantly, grade 4 toxicity with SJS-like presentation might have a protracted course, requiring close observation of rashes that fail to respond to dermatologic treatment.[22]

Dermatologists have an important role in providing specialized care to oncologic patients with toxicities from their treatments. Cutaneous irAE from immune checkpoint inhibitor therapy are among the most frequently reported and might result in interruption of cancer treatment in severe cases. With proper assessment and prompt management, most inflammatory eruptions could be effectively treated without interruption of immunotherapy.

Limitations

This was a retrospective, single-institutional study. Patients were only evaluated if they were

referred to our oncodermatology clinic within the cancer center or seen by the inpatient consultative service, whereas mild eruptions that responded to topical therapy provided by medical oncologists or self-limiting eruptions were probably not seen. Thus, our cohort might represent the more severe inflammatory eruptions at our institution.

CONCLUSIONS

Over the course of 2 years, 103 inflammatory eruptions that developed during checkpoint inhibitor therapy were referred to oncodermatology or inpatient consultative service at our institution and stratified according to toxicity. Of the severe reactions (grade 3 or 4) that required interruption of checkpoint inhibitor therapy, immunobullous and exfoliative presentations were most frequent. Most rashes (13/16) that required temporary interruption of immunotherapy resolved or were well controlled on dermatologic therapy, but 3 of 16 (18.8%) developed a grade 2 or 3 flare on rechallenge. Additional prospective studies are needed to further evaluate the prognostic relevance of these specific rash types.

REFERENCES

1. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti—PD-1 antibody in cancer. *N Engl J Med*. 2012;366(26):2443-2454.
2. Sundar R, Cho B-C, Brahmer JR, Soo RA. Nivolumab in NSCLC: latest evidence and clinical potential. *Ther Adv Med Oncol*. 2015;7(2):85-96.
3. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363(8):711-723.
4. Haanen JBAG, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(suppl_4):iv119-iv142.
5. Weber JS, Yang JC, Atkins MB, Disis ML. Toxicities of immunotherapy for the practitioner. *J Clin Oncol*. 2015;33(18):2092-2099.
6. Villadolid J, Amin A. Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. *Transl Lung Cancer Res*. 2015;4(5):560-575.
7. Curry JL, Tetzlaff MT, Nagarajan P, et al. Diverse types of dermatologic toxicities from immune checkpoint blockade therapy. *J Cutan Pathol*. 2017;44(2):158-176.
8. Belum VR, Benhuri B, Postow MA, et al. Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. *Eur J Cancer*. 2016;60:12-25.
9. Shi VJ, Rodic N, Gettinger S, et al. Clinical and histologic features of lichenoid mucocutaneous eruptions due to anti-programmed cell death 1 and anti-programmed cell death ligand 1 immunotherapy. *JAMA Dermatol*. 2016;152(10):1128-1136.
10. Hwang SJE, Carlos G, Wakade D, et al. Cutaneous adverse events (AEs) of anti-programmed cell death (PD)-1 therapy in patients with metastatic melanoma: a single-institution cohort. *J Am Acad Dermatol*. 2016;74(3):455-461.e1.
11. Goldinger SM, Stieger P, Meier B, et al. Cytotoxic cutaneous adverse drug reactions during anti-PD-1 therapy. *Clin Cancer Res*. 2016;22(16):4023-4029.
12. Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann Oncol*. 2015;26(12):2375-2391.
13. Kaunitz GJ, Loss M, Rizvi H, et al. Cutaneous eruptions in patients receiving immune checkpoint blockade: clinicopathologic analysis of the nonlichenoid histologic pattern. *Am J Surg Pathol*. 2017;41(10):1381-1389.
14. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373(1):23-34.
15. Damsky W, Kole L, Tomayko MM. Development of bullous pemphigoid during nivolumab therapy. *JAAD Case Rep*. 2016;2(6):442-444.
16. Siegel J, Totonchy M, Damsky W, et al. Bullous disorders associated with anti-PD-1 and anti-PD-L1 therapy: a retrospective analysis evaluating the clinical and histopathologic features, frequency, and impact on cancer therapy. *J Am Acad Dermatol*. 2018;79(6):1081-1088.
17. Suozzi KC, Stahl M, Ko CJ, et al. Immune-related sarcoidosis observed in combination ipilimumab and nivolumab therapy. *JAAD Case Rep*. 2016;2(3):264-268.
18. Coleman E, Panse G, Haldas J, Gettinger S, Leventhal JS. Pityriasis rubra pilaris-like erythroderma in the setting of pembrolizumab therapy responsive to acitretin. *JAAD Case Rep*. 2018;4(7):669-671.
19. Charollais R, Aubin F, Roche-Kubler B, Puzenat E. Two cases of granuloma annulare under anti-PD1 therapy. *Ann Dermatol Venereol*. 2018;145(2):116-119.
20. Hwang SJE, Carlos G, Wakade D, Sharma R, Fernandez-Penas P. Ipilimumab-induced acute generalized exanthematous pustulosis in a patient with metastatic melanoma. *Melanoma Res*. 2016;26(4):417-420.
21. Page B, Borradori L, Beltraminelli H, Yawalkar N, Hunger RE. Acute generalized exanthematous pustulosis associated with ipilimumab and nivolumab. *J Eur Acad Dermatol Venereol*. 2018;32(7):e256-e257.
22. Vivar KL, Deschaine M, Messina J, et al. Epidermal programmed cell death-ligand 1 expression in TEN associated with nivolumab therapy. *J Cutan Pathol*. 2017;44(4):381-384.